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Incidence of Female Breast Cancer among Atomic Bomb Survivors, 1950–1985

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An incidence survey among atomic bomb survivors identified 807 breast cancer cases, and 20 second breast cancers. As in earlier surveys of the Life Span Study population, a strongly linear radiation dose response was found, with the highest dose-specific excess relative risk (ERR) among survivors under 20 years old at the time of the bombings. Sixty-eight of the cases were under 10 years old at exposure, strengthening earlier reports of a marked excess risk associated with exposure during infancy and childhood. A much lower, but marginally significant, dose response was seen among women exposed at 40 years and older. It was not possible, however, to discriminate statistically between age at exposure and age at observation for risk as the more important determinant of ERR per unit dose. A 13-fold ERR at 1 Sv was found for breast cancer occurring before age 35, compared to a 2-fold excess after age 35, among survivors exposed before age 20. This *a posteriori* finding, based on 27 exposed, known-dose, early-onset cases, suggests the possible existence of a susceptible genetic subgroup. Further studies, involving family histories of cancer and investigations at the molecular level, are suggested to determine whether such a subgroup exists.

INTRODUCTION

This is the fourth in a series of reports *(1–3)* on incidence of breast cancer in females and radiation dose in the Life Span Study (LSS)[2] sample, a defined population of survivors of the atomic bombings of Hiroshima and Nagasaki, Japan. With the present report, follow-up is extended through the end of 1985. The number of incident cases is increased through longer follow-up and, to a lesser extent, by an expansion of the low-dose portion of the Nagasaki component of the sample *(4)*, and risks are evaluated using Dosimetry System 1986 (DS86), which replaced the previous system, the tentative 1965 dosimetry system (T65D), in 1986 *(5, 6)*.

The previous survey *(3)* covered the period from October 1, 1950, the date of the census upon which selection of the study population was based *(7)*, through December 31, 1980. In that study, 564 cases were identified, 10 of them bilateral. Dose–response analyses using the T65D dosimetry found a highly significant linear increase in incidence with increasing dose, which was statistically significant even over the restricted dose range of 0–0.5 Gy for the breast. A significant dose response, based on 24 cases, was found for subjects exposed before age 10 *(3, 8)*. That finding was substantiated by Hildreth *et al. (9, 10)*, who observed a similar excess among women irradiated in infancy for a supposedly enlarged thymus. In general, the level of dose response was strongly and significantly dependent upon age at the time of the bombings (ATB): the estimated excess relative risk (ERR) per Gy was 5.3, 2.6, 1.2, 0.0 and 0.4, respectively, for women age 0–9, 10–19, 20–39, 40–49 and 50 or older ATB. In all age cohorts in which a dose-related excess risk was demonstrated, that risk was not apparent until at least 10 years after exposure and not before (about) age 30, and the relative risk subsequently was fairly constant over time since exposure. The incidence of second breast (bilateral) cancers also increased with increasing dose, but there was no evidence that they tended to occur in a subgroup particularly sensitive to radiation.

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[2] Abbreviations used: ATB, at the time of the bombings; DS86, Dosimetry System 1986; ERR, excess relative risk; ICD, International Classification of Disease; LSS, Life Span Study; NIC, not in city; PY, person-years; RBE, relative biological effectiveness; RERF, Radiation Effects Research Foundation; RR, relative risk; T65D, tentative 1965 dosimetry system.

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MATERIALS AND METHODS

Information on possible breast cancer cases among female members of the LSS sample (70,165 women in 1950) was provided by the Tumor and Tissue Registry Office of the Radiation Effects Research Foundation (RERF), which searched the LSS Tumor Registry, the local (i.e., Hiroshima and Nagasaki) tumor and tissue registries, the RERF autopsy series and the death certificate series as described in RERF *Guidelines for the Conduct of Site-specific Cancer Incidence Studies (11).* The local registries are population-based and routinely contribute cases from the locally resident portion of the LSS population to the LSS registry. The search also included the files of local hospitals and clinics known to treat breast cancer but whose contributions to the registries, for one reason or another, have not been complete. As in the previous breast cancer series *(1–3),* special efforts were made to ascertain cases diagnosed before the Hiroshima and Nagasaki tumor registries were initiated in 1957 and 1958, respectively.

Virtually complete ascertainment of death and of cause of death as recorded on the death certificate is obtained by RERF for LSS sample members through the Japanese family-registry system. All death certificates having International Classification of Disease (ICD, 9th revision codes) 174, 175, 217, 233, 238-3 and 239-3 were reviewed, and inquiries were made at the hospital at which death occurred in cases for which adequate information from other sources was not already available. Death certificates from the years 1986–1989 were included in the review to identify cases whose initial diagnoses occurred before 1986. Death certificates for LSS members who had emigrated from the contacting area for the local tumor and tissue registries to other parts of Japan were followed up through inquiries to the hospitals where death occurred, and loans of pathological materials were requested. Clinical findings and data on the pathology, including histological sections, were sought for all cases identified in the initial ascertainment. When available, information taken from reviews of medical charts of individual cases was recorded for possible later analysis; such information included tumor size, location and metastasis, extent of the primary tumor, history of benign breast disease, malignancy in other organs, method of therapy, and marital and childbearing histories. Cases were reviewed on the basis of available materials and, if accepted, were assigned diagnostic certainty ratings on a 1–4 scale as follows: (1) death certificate only, (2) clinical diagnosis only, or clinical diagnosis and death certificate information, (3) pathological diagnosis but materials not available for review by the present investigators, and (4) pathological review by the present investigators. Following the practice used in the previous series and in a binational review of some 300 cancers in 1979 *(12),* cases were classified according to the histological criteria proposed by the World Health Organization *(13)* and the Japanese Mammary Cancer Society *(14).* All breast cancer material was reviewed without knowledge of exposure or dose. Cases included in the previous LSS series *(3)* were included in the present series unless new information dictated otherwise. Cases with new diagnostic materials were treated the same as cases identified for the first time in the present study.

Ascertainment of cases for the present study differed in several ways from a concurrent survey of solid cancer incidence based on the RERF Tumor Registry *(15).* That study separately addressed cancers of the breast and of various other sites, although necessarily more briefly than was possible here. Incidence coverage was limited to locally resident, exposed members of the LSS sample with DS86 kerma under 4 Gy, and covered the period 1958–1987. The present study covered the period 1950–1985, for all members of the LSS sample, and included a review of diagnostic information independent of that carried out by the tumor registry.

Statistical Analysis

The AMFIT algorithm *(16)* for unconditional, Poisson-model, maximum-likelihood regression of grouped survival data was used to test for the existence of dose-related ascertainment bias as described in the Results section, to estimate the possible dependence of risk on radiation dose, and to evaluate the variation of the level of dose response with respect to city, age ATB, sex, time since exposure and attained age. These analyses were based on numbers of cases and person-years (PY) of observation for risk, the latter accumulated through the date of diagnosis of (first) breast cancer for cases and to the date of death or 31 December 1985, for noncases. Numbers of cases and PY were grouped by interval of breast tissue dose, city of exposure (Hiroshima or Nagasaki), age ATB in 5-year intervals to age 55, plus 55 and older, attained age in 5-year intervals from age 30 through 79, plus intervals for lower and higher ages, and calendar year: 1950–1955, 1956–1957, 1958–1960, and 5-year intervals from 1961 through 1985 (the interval 1956–1960 was split because the tumor registries began in 1957–1958). Rates were analyzed with respect to average organ equivalent dose in sieverts, assuming a constant relative biological effectiveness (RBE) of 10 for neutrons, as in other recent RERF reports *(4, 15).* Thus, for example, the excess breast cancer incidence corresponding to a neutron-only dose of 0.1 Gy or a γ-ray-only dose of 1 Gy are assumed to be the same. Equivalent dose mean values, in sieverts, were computed for each cell in the above cross-classification. Separate γ-ray and neutron coefficients were not estimated because DS86 neutron doses are too low, and too highly correlated with γ-ray dose within cities, to yield statistically stable estimates. No adjustment was made for random error in individual dose estimates. In what follows, "dose" will be used to refer to both breast tissue equivalent dose in sieverts (the relevant quantity for risk estimation) and breast tissue dose in grays; the meaning will be clear from the context.

Dose-related breast cancer risk was estimated relative to baseline incidence, using stratified relative risk (RR) models in which a saturated loglinear model was used to estimate rates per PY at zero dose in 2304 strata defined by the two cities, 12 age ATB intevals, 12 attained-age intervals and 8 calendar periods. Other analyses, in which the logarithm of the rate at zero dose was modeled as a linear function of city and the logarithms of attained age and time since exposure, were used to estimate absolute excess risk, i.e., the number of excess cases per 10^4 persons per year per sievert. As shown in the previous report *(3),* however, estimates of absolute excess risk, unlike relative risk, depend heavily on assumptions about minimal latent period and are likely to be biased downward because of underascertainment of cases among that part of the study cohort that has emigrated from Hiroshima and Nagasaki. Such emigration is known to have occurred differentially by city, sex and age ATB, but not by radiation dose *(3, 15).* The problem of adjustment of PY denominators for migration was addressed in the report on the previous series *(3),* to which the reader is referred for details. The results of that analysis indicated that estimates of dose-related relative risk in this population are virtually unaffected by adjustment for migration. The approach used in the recent tumor registry report *(15),* in which cases were limited to cohort members resident in Hiroshima and Nagasaki, provides a more secure basis for absolute risk estimates. Thus, in the present report, absolute risk estimates are used sparingly, and for limited purposes, while relative risk estimates are presented with reasonable confidence that they truly represent underlying patterns of risk.

The basic regression model for most analyses reported here was of the form,

$$\mathrm{RR}\ (D; z_1, \ldots, z_i) = 1 + \alpha D \exp\ (\Sigma \beta_i z_i), \qquad (1)$$

where α and the β_i denote unknown parameters describing the dependence of ERR on dose D and modifying factors represented by $z_1, \ldots, z_j$ such as age ATB, attained age and time after exposure.

Treatment of the nonexposed, or not-in-city (NIC), portion of the LSS cohort has been controversial. For example, the NIC have not been included as part of the zero-dose group in most of the periodic LSS mortality reports, or in the recent tumor registry report *(15),* because it was

TABLE I
Distribution of Newly Ascertained Cases (and Second Cancers, in Parentheses) by Series, Population and Period

	Series, period of coverage and population sample						
					Present series		
Period	Wanebo (1950–1966) clinical subsample	McGregor (1950–1969) LSS[a]	Tokunaga (1950–1974) LSS	Tokunaga (1950–1980) LSS	LSS	1985 LSS expansion	Total
1950–1966	25	152 (1)	15	7	4	20	223 (1)
1967–1969		37 (1)	27	3	2 (1)	3	72 (2)
1970–1974			96	23 (1)	1 (1)	4	124 (2)
1975–1980				167 (7)	23 (1)	8 (1)	198 (9)
1981–1985				1[b]	176 (5)	13 (1)	190 (6)
1950–1985 total	25	189 (2)	138	201 (8)	206 (8)	48 (2)	807 (20)

Note. The "1985 expansion" is an increase in the LSS sample.
[a]LSS = Life span study.
[b]Additional information resulted in a change of the diagnosis date from December 1980 to January 1981.

felt that sociological differences between the NIC and exposed portions of the sample might be a potential source of bias *(17).* However, many of the comparisons appropriate for an incidence study are concerned less with the magnitude of the dose response than with its variation over time, by age ATB and by attained age; such comparisons, because of their detail, may benefit from having the increased numbers of cases at low dose levels obtained by including observations on the NIC part of the LSS population. This consideration is still important, even with the recent inclusion in the population of additional distally exposed survivors in Nagasaki *(4).* The approach taken in the present investigation was to conduct parallel analyses, with and without the NIC data, and to present results based on the larger data set only if they differed meaningfully from those based on the exposed subjects alone, or to correct statistical instability due to small numbers of low-dose cases.

All reported *P* values are two-tailed, based on likelihood-ratio tests. Point estimates are presented with two-sided, equi-tailed, likelihood-ratio confidence intervals, in most cases at confidence level 0.90 corresponding to one-sided hypothesis tests at level 0.05.

RESULTS

Case Ascertainment

In all, 807 breast cancer cases, 20 of them bilateral, were included in the series. Of the 827 breast cancers (807 first cancers plus 20 second cancers, i.e., cancers in the second breast, whether diagnosed simultaneously with the first, or later), 635 were accepted on the basis of pathology review by the present investigators, 88 on the basis of review by other pathologists, 54 on the basis of clinical information and 50 on the basis of death certificate information only. The ascertainment did not appear to be biased with respect to dose, on the basis of the following analyses: (1) There was no statistical association between the basis of acceptance of breast cancer diagnosis and dose. (2) Within dose intervals, the proportion of cases from the clinical subsample of the LSS cohort, in which the higher-dose subjects are disproportionately represented and whose members are solicited every 2 years for medical examinations at RERF, was consistent with uniform ascertainment levels. (3) The dose distribution of cases was statistically similar to that of death certificate diagnoses of breast cancer for the same period, as reported by Shimizu *et al. (4);* ascertainment of death certificates is virtually complete and therefore unbiased.

Relationship to Earlier Series

As shown in Table I, 25 of the 807 cases in the present series were first identified by Wanebo *et al. (18)* in their initial study of breast cancer incidence in the clinical subsample of the LSS cohort during 1950–1966. Another 189 cases, and 2 second breast cancers, were found by McGregor *et al. (1)* in their study based on the entire cohort for the period 1950–1969. Tokunaga *et al. (2)* extended follow-up through September 1974, identifying another 138 cases but no further second breast cancers; later *(3),* follow-up was extended through 1980, with an additional ascertainment of 201 cases and 8 second breast cancers. The current series contributed 254 new cases and 10 second breast cancers; 48 of the cases and 50 of the total breast cancers correspond to an expansion of the LSS cohort by 11,393 survivors of both sexes, exposed in Nagasaki at distances from the hypocenter of 2500 m or greater *(4).* With continued follow-up, information has accumulated on cases already in the series or previously considered, and rejected, as possible cases; a few have been added or dropped because of new information. Evidence of delays in the case ascertainment process can be seen in the distribution of cases by study and period (Table I). The numbers reflect delays in transmitting information to the tumor registry about cases within the registry's catchment area. These numbers also reflect cases, diagnosed in other parts of Japan, that came to the attention of RERF only because breast cancers that may have been diagnosed and treated many years earlier were mentioned on death certificates or because the patient later returned to the Hiroshima or Nagasaki area and was examined at a local hospital or clinic.

TABLE II
Distribution of Cases (and Second Cancers, in Parentheses) by Age ATB and Period

Period	Age ATB (years) 0–9	10–19	20–29	30–39	40–49	>=50	Total cases	Crude rate: cases per 10^4PY
1950–1955		2	4	9	16	11	42	1.16
1956–1957			4	10	5	5	24	1.79
1958–1960		2	3	11	13	11	40	2.04
1961–1965		17	33	26 (1)	10	14	100 (1)	3.18
1966–1970	4	28 (1)	34 (1)	23	16	8	113 (2)	3.78
1971–1975	10	53 (2)	28 (1)	22	18	4	135 (3)	4.79
1976–1980	16 (1)	64 (4)	35 (1)	25 (2)	19	4	163 (8)	6.18
1981–1985	38 (1)	64 (2)	42 (2)	32	14 (1)		190 (6)	7.77
Total	68 (2)	230 (9)	183 (5)	158 (3)	111 (1)	57	807 (20)	3.85
Women	12,004	14,541	11,956	11,323	10,134	10,207	70,165	

Note: ATB = at the time of the bombings.

Ascertainment by Age ATB, Age at Diagnosis and Period

As shown in Table II, in recent years incident cases have increasingly come from the younger age-ATB groups. In all, there were 68 cases (and 2 second breast cancers) in the group 0–9 years old ATB, 230 (9) in the 10–19 group, 183 (5) in the 20–29 group, 158 (3) in the 30–39 group, 111 (1) in the 40–49 group and 57 (0) in the group exposed when older. Not surprisingly, the younger cohorts became increasingly important to the overall experience in recent years: 54% of all cases, and cancers, diagnosed during 1981–1985 occurred among women under 20 ATB. No marked increase in annual case ascertainment was seen after establishment of the tumor registries in 1957–1958. However, evidence of a gradual increase over time was seen as the younger members of the cohort reached ages at which rates normally increase (Table III). The extremely low crude rate for the 0–9 ATB cohort reflects the fact that, in 1950, when follow-up began, these women were between 5 and 15 years old and another 10 years were required before even the oldest reached ages at which breast cancer normally occurs. In the sample as a whole, only five cases were diagnosed at ages under 30. Crude rates increased with increasing attained age, reaching an apparent plateau at ages 40–44. These rates do not reflect only attained age; most observations at early ages pertained to the younger birth cohorts, and most observations at later ages pertained to women in the older cohorts. Thus, given the likelihood of secular trends in age-specific rates, the apparent plateau in Table III may have no significance in terms of dependence of risk on attained age *per se.*

TABLE III
Distribution of Cases (and Second Cancers, in Parentheses) by Age ATB and Attained Age

Attained age (years)	Age ATB (years) 0–9	10–19	20–29	30–39	40–49	≥50	Total cases	Crude rate: cases per 10^4PY
<30	1	4					5	0.13
30–34	15	16	2				33	1.88
35–39	15 (2)	25	15				55 (2)	2.75
40–44	27	43 (1)	30 (1)	10			110 (2)	5.18
45–49	10	63 (6)	31	23 (1)	3		130 (7)	6.30
50–54		55 (2)	26 (1)	22	13		116 (3)	5.66
55–59		23	39	26	13	2	103	6.60
60–64		1	34 (3)	21 (2)	16	3	75 (5)	4.80
65–69			6	22	15	16	59	4.47
70–74				24	20	11	55	5.61
75–79				10	17	8	35	4.89
>=80					14 (1)	17	31 (1)	5.38
All ages	68 (2)	230 (9)	183 (5)	158 (3)	111 (1)	57	807 (20)	3.85
Crude rate: cases/10^4PY	1.63	4.66	4.61	4.44	4.07	3.55	3.85	

Note: ATB = at the time of the bombings.

TABLE IV
Distribution of Women and Breast Cancer Cases by City, Exposure Group and Radiation Dose

		Exposure group										
		Dose interval: breast tissue dose (Gy)										
	Not in city	<0.001	0.001–0.009	0.01–0.099	0.1–0.249	0.25–0.49	0.5–0.99	1.0–1.99	2.0–2.99	3.0–3.99	4.0–6.0	Unknown
Combined Cities												
Mean dose (Gy)												
γ-rays		0.0000	0.0065	0.035	0.16	0.35	0.69	1.37	2.35	3.28	4.73	—
Neutrons		0.0000	0.0000	0.0000	0.0012	0.0033	0.0089	0.025	0.053	0.095	0.14	—
Mean equivalent dose (Sv)		0.0000	0.0065	0.035	0.17	0.38	0.78	1.62	2.88	4.23	6.08	—
Women	15,411	19,649	6587	13,658	4553	2991	2063	996	280	73	96	3908
Cases	143	193	60	132	55	46	51	28	14	2	10	73
RR[a]	0.86	1.00	0.96	0.96	1.15	1.48	1.35	2.75	5.02	2.62	11.39	1.78
RR 90% CI	0.71–1.03	—	0.75–1.22	0.79–1.15	0.88–1.47	1.12–1.92	1.80–3.03	1.94–3.79	3.08–7.70	0.62–7.02	6.37–18.69	1.41–2.23
Rate[b]	2.8	3.3	3.2	3.2	3.8	4.9	7.8	9.2	16.6	8.5	38.3	6.1
Hiroshima												
Mean dose (Gy)												
γ rays		0.0000	0.0069	0.039	0.16	0.35	0.68	1.38	2.32	3.26	4.61	—
Neutrons		0.0000	0.0000	0.0000	0.0016	0.0050	0.013	0.038	0.079	0.13	0.21	—
Equivalent dose (Sv)		0.0000	0.0069	0.039	0.17	0.40	0.81	1.77	3.11	4.61	6.71	—
Women	11,392	11,860	3707	10,209	3853	2452	1478	645	212	54	65	1935
Cases	121	130	42	110	46	40	33	18	13	2	8	43
Rate[b]	3.3	3.7	3.9	3.7	4.1	5.6	7.5	9.6	21.8	11.7	46.6	6.6
Nagasaki												
Mean dose (Gy)												
γ rays		0.0000	0.0061	0.032	0.17	0.35	0.71	1.35	2.38	3.30	4.86	—
Neutrons		0.0000	0.0000	0.0000	0.0007	0.0016	0.0046	0.011	0.023	0.035	0.055	—
Equivalent dose (Sv)		0.0000	0.0061	0.032	0.17	0.36	0.75	1.46	2.61	3.65	5.41	—
Women	3479	7789	2880	3449	700	539	585	351	68	19	31	1873
Cases	22	63	18	22	9	6	18	10	1	0	2	30
Rateb	2.0	2.7	2.1	2.2	4.2	3.6	9.4	8.8	4.8	0	24.0	5.2

[a] Adjusted for city, age at the time of the bombings, attained age and time since exposure. RR = relative risk.

[b] Cases per 10^4 PY, indirectly standardized to the PY distribution of the <0.001 Gy group with respect to city, age at the time of the bombings, attained age and time since exposure.

Dose–Response Analyses

Of the 807 cases, 143 were among the NIC, 73 were exposed but without DS86 dose estimates, and the remaining 591 had dose estimates between 0 and 6 Gy to breast tissue (Table IV). Estimated RRs and incidence rates, adjusted for city, age ATB, attained age and year, and standardized on the zero-dose exposed group, are given by dose and/or exposure group. Breast cancer incidence was nonsignificantly lower ($P = 0.18$) in the NIC group than in the zero-dose group. Risk was significantly elevated in the "unknown-dose" group, for which DS86 doses could not be calculated, to a level consistent with an average (equivalent) dose of about 0.5 Sv.

Risk was strongly associated with estimated breast tissue dose. Age-adjusted ERR per Sv, estimated by fitting a linear model and assuming no appreciable dose-related excess before about 12 years after exposure (i.e., before January 1958), was 1.56 with 90% confidence limits of 1.19, 1.99 if the NIC data were included in the zero-dose standard, and 1.50 (1.12, 1.94) if the NIC were excluded (Fig. 1). Thus inclusion or exclusion of the NIC made little difference to the dose–response analysis. (In what follows, unless specifically stated otherwise, results presented have been obtained from the exposed, known-dose part of the study population. Except as noted in the text, dose–response results were not markedly different when the NIC data were included.)

The observed dose response was highly consistent with a linear model. The difference in deviance compared to an unconstrained dose response based on 10 dose intervals was only 4.59 with 8 degrees of freedom (df) ($P = 0.80$). Adding a dose-squared term to the linear model did not improve

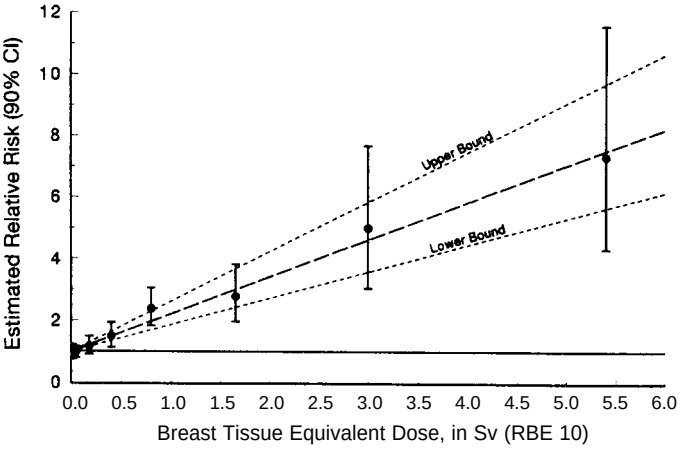

FIG. 1. Estimated relative risk, with 90% confidence limits, by mean estimated equivalent dose (neutron RBE = 10) to breast tissue; for consecutive dose intervals (Table IV) and fitted linear dose–response model; exposed women only, stratified on city, age at the time of the bombings, attained age and calendar time.

the fit significantly *(P* = 0.92). In the quadratic model,

$$RR = 1 + \alpha D (1 + \beta D), \quad (2)$$

where *D* is equivalent dose in sieverts, the point estimate for β was 0.0055 with 90% confidence interval –0.077, 0.19. Thus the lowest crossover dose consistent with the data, i.e., the lowest dose at which the contributions of *D* and D^2 are equal, was $(0.19)^{-1} = 5.25$ Sv.

The estimated ERR per Sv was little affected by disregarding high-dose data and remained significantly greater than zero until all observations on subjects with breast tissue doses above 0.25 Gy had been deleted (Table V). These grouped data provide direct evidence of a positive dose response below 0.5 Gy (the mean dose was 0.38 Sv for the 0.25–0.49-Gy interval) but fail to do so below 0.25 Gy (the mean dose for the 0.1–0.24-Gy interval was 0.17 Sv).

Second Breast Cancers

Of the 20 second breast cancers observed, 2 were in the NIC group and 3 were in the group without DS86 dose estimates. The estimated ERR of a second breast cancer was 1.37 per Sv (0.08, 4.71), virtually the same as the estimate of 1.50 for first cancers. The proportion of *cases* with second cancers was not related to dose *(P* = 0.52 for trend in a binomial model analysis restricted to breast cancer cases). In other words, the mean estimated dose among cases with second breast cancers was higher than that for the population as a whole, but was similar to that among cases with only one affected breast.

TABLE V
Summary of Linear Dose–Response Analyses for Dose Intervals Bounded from Above

Maximum breast tissue dose (Gy)	Estimated excess relative risk per Sv	90% confidence limits
6.0	1.50	1.12, 1.94
3.99	1.43	1.03, 1.89
2.99	1.53	1.11, 2.03
1.99	1.52	1.05, 2.07
0.99	1.73	1.10, 2.48
0.49	1.31	0.41, 2.40
0.249	0.87	–0.70, 2.82
0.099	– 1.58	–6.03, 3.76

Expression Period

The time required before the appearance of an appreciable excess risk was estimated by fitting the linear model, $RR = 1 + \alpha D$, which assumes a constant ERR over time at any given dose, with the constraint $\alpha = 0$ for any period earlier than 1950, 1956, 1958, 1961 or 1966; these dates correspond to the beginnings of the earliest intervals into which the data were divided. The corresponding deviance reduction values, compared to a zero-dose response, were 94.8, 95.3, 100.8, 96.4 and 83.9, respectively. Thus choosing January 1, 1958, as the approximate beginning of the expression period for breast cancer incidence associated with exposure to atomic bomb (A-bomb) radiation, at least among women old enough to have had an appreciable baseline breast cancer risk at that time, corresponds to a deviance difference of 4.4 or more compared with any other of the possibilities considered. Moreover, the estimated slope obtained by restricting consideration to the period 1950–1957 was negative, whereas it was positive for all later periods. (Of 23 cases diagnosed in 1956–1957 with dose estimates, none had over 0.5 Gy, and only one had over 0.1 Gy.) The distribution of cases by year of diagnosis (Table II) does not suggest that this rough determination of an expression period of about 12 years is an artifact of improvements in ascertainment efficiency associated with the establishment of the tumor registries in 1957 (Hiroshima) and 1958 (Nagasaki) or of the beginning, in 1958, of routine, biennial medical examinations of the clinical subsample.

Only 5 cases were diagnosed at ages under 30, as follows:

Case no .	City	Age ATB	Age at diagnosis	Year of diagnosis	Equivalent dose
044852	Nagasaki	16	25	1954	0 (NIC)
241017	Hiroshima	17	24	1952	0.41 Sv
266389	Hiroshima	1	29	1973	0.01 Sv
266952	Hiroshima	12	28	1961	0.24 Sv
294151	Hiroshima	13	28	1961	Unknown

These data provide little basis for estimating a minimum

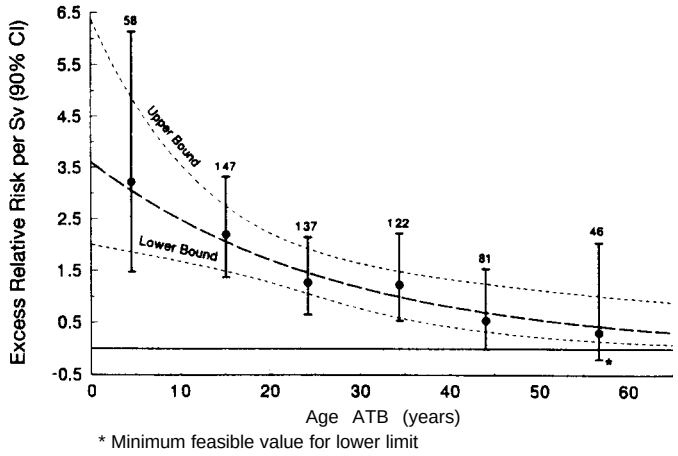

FIG. 2. Estimated excess relative risk per Sv, by interval of age at the time of the bombings (age ATB) (0–9, 10–19, 20–29, 30–39, 40–49 and >=50), with fitted model ERR $(D;E) = \alpha D \exp(\beta_i E)$, where D is equivalent dose in Sv (neutron RBE = 10) and E is age ATB. Estimates and 90% confidence limits stratified on city, age ATB, attained age and period. Total number of cases appears above the upper confidence limit for each interval of age ATB.

age (as opposed to time interval) for the appearance of radiation-induced breast cancer; estimates of ERR per Sv, even when restricted to women younger than 20 years ATB, were virtually unaffected by inclusion or exclusion of data pertaining to attained ages under 30 years. (Exclusion did, of course, influence estimates of absolute risk, since a substantial proportion of PY among those under 12 years ATB were experienced after 1957 and at attained ages under 24, when no cases occurred.)

City Differences

Breast cancer rates were generally about 25% lower in Nagasaki than in Hiroshima (Table IV). In terms of ERR per Sv, however, the fitted linear coefficients were statistically indistinguishable ($P = 0.48$): the slope estimate was 1.40 (1.00, 1.89) for Hiroshima and 1.85 (1.02, 2.99) for Nagasaki. Additive model estimates were also similar ($P = 0.73$) for the two cities: 6.4 (4.7, 8.2) excess cases per 10^4 per Sv for Hiroshima vs 7.1 (4.3, 10.4) for Nagasaki, when cases diagnosed before age 30 were ignored; the estimates were almost identical when the slope estimates were adjusted for age ATB.

Age ATB, Attained Age and Time since Exposure

The ERR per Sv depended heavily upon age ATB (Fig. 2, Table VI), decreasing by an estimated 3.7% (1.4%, 6.2%) per additional year. That estimate corresponds to the fitted model,

$$\mathrm{RR}(D;E) = 1 + 3.60\, D \exp(-0.0374\, E), \qquad (3)$$

where D is breast tissue dose in Sv and E is age ATB in years; the semicolon in RR $(D;E)$ is used here and elsewhere to indicate that E is an exponential modifier of the linear coefficient for D. There was no significant difference in fit between this continuous model and the step models corresponding to the age-specific estimates in Fig. 2 and Table VI. Essentially the same level of fit was obtained by specifying ERR to be a step function over the age ranges 0–19, 20–39 and >=40 years ATB; estimated values were 2.41 (1.63, 3.44), 1.25 (0.77, 1.87) and 0.48 (0.002, 1.28) per Sv, respectively. Thus a marginally statistically significant ERR (one-tailed $P < 0.05$) was found for the group >=40 years ATB (it can be argued that a one-tailed significance test is appropriate here, since the alternative of a negative dose response has little credibility).

TABLE VI
Dependence of Dose Response on Age-ATB Interval: Excess Relative Risk (ERR) per Sievert

Age ATB	ERR	90% CI	ERR	90% CI	ERR	90% CI
0–4	4.64	1.68, 11.23	3.21	1.47, 6.13		
5–9	2.08	0.29, 5.61			2.41	1.63, 3.44
10–14	1.82	0.79, 3.50	2.19	1.37, 3.31		
15–19	2.49	1.36, 4.17				
20–24	1.18	0.48, 2.27	1.27	0.65, 2.14		
25–29	1.45	0.42, 3.15			1.25	0.77, 1.87
30–34	0.96	0.21, 2.23	1.23	0.54, 2.22		
35–39	1.60	0.51, 3.52				
40–44	0.02	NC,[a] 0.91	0.54	–0.01, 1.54		
45–49	1.78	0.30, 5.03			0.48	0.002, 1.28
50–54	0.51	NC, 3.24	0.31	NC, 2.04		
>=55	–0.12	NC, 2.98				
Deviance (df)[b]	13.64 (11)		8.99 (5)		8.36 (2)	

[a] NC: Confidence limit could not be calculated.

[b] Improvement in deviance over a common linear dose response for all ages at the time of the bombings (ATB).

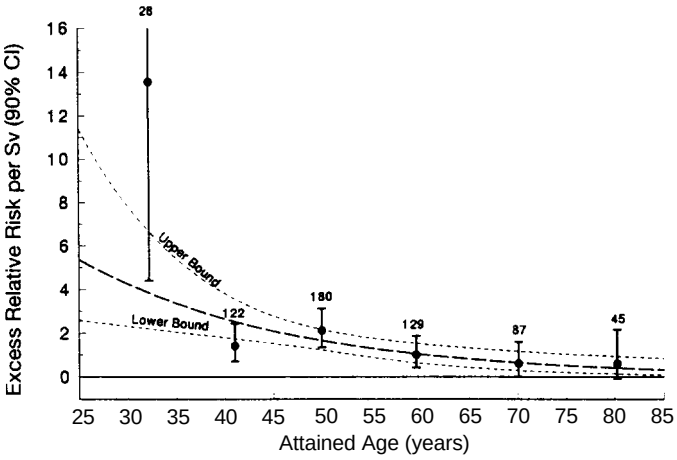

FIG. 3. Estimated excess relative risk per Sv, by interval of attained age (25–34, 35–44, 45–54, 55–64, 65–74 and >=75), with fitted model ERR $(D;A) = \alpha\, D \exp(\beta_2 A)$, where D is equivalent dose in Sv (neutron RBE = 10) and A is attained age. Estimates and 90% confidence limits stratified on city, age at the time of the bombings, attained age and period. Total number of cases appears above the upper confidence limit for each interval of attained age.

Radiation-related risk was also strongly dependent upon attained age (Fig. 3, Table VII). The ERR per Sv decreased by an estimated 4.6% (2.0%, 7.6%) for each additional year, corresponding to the model

$$\mathrm{RR}\,(D;A) = 1 + 1.65\, D \exp[-0.047\,(A - 50)], \qquad (4)$$

where A is attained age. The most remarkable feature of Fig. 3, however, is that ERR per Sv was substantially higher for cancers diagnosed before age 35 than at higher ages. (The ERR for attained ages 35–39 was similar to that for older ages.) In an analysis suggested by the figure, the level of deviance was reduced by 4.5 (= 13.71 – 9.24; see Table VII) by adding a parameter for attained age less than 35:

$$\mathrm{RR}\,[\,D;A,I_{<35}(A)\,] = 1 + 1.52\ \mathrm{D} \exp[-0.032\,(A - 50) + 1.64\, I_{<35}(A)\,] \qquad (5)$$

where $I_{<35}(A) = 1$ for $A < 35$ and $= 0$ otherwise. The additional contribution of attained age *per se* was similar: a deviance reduction of 4.1 (13.71 – 9.63) corresponding to $P = 0.043$, assuming a χ^2 distribution with 1 df. In analyses restricted to risk at attained ages of 35 years or more, it was impossible to separate the effects of age ATB and attained age (these results can be readily inferred from Table VII).

When age ATB and attained age, the latter as represented by the variables A and/or $I_{<35}(A)$ defined above, were included in the same model, the results were as follows (Table VII): The model RR $(D;E,A)$ provided a significant deviance reduction (dev) over neither RR $(D;A)$ (dev = 9.44 – 9.24 = 0.20, $P = 0.65$) nor RR $(D;E)$ (dev = 9.44 – 7.28 = 2.16, $P = 0.14$), nor was RR$[\,D;E,A,I_{<35}(A)\,]$ a significant improvement over RR$[\,D;A,I_{<35}(A)\,]$ (dev = 14.10 – 13.71 = 0.39, $P = 0.53$) or RR$[\,D;E,I_{<35}(A)\,]$ (dev = 14.10 – 13.59 = 0.51, $P = 0.48$). Thus age ATB (E) and attained age (A) were so closely correlated that their respective relationships to radiation-associated risk could not be disentangled, especially after allowing for the possibility of increased risk of breast cancer diagnosed before age 35. But RR$[\,D;E,I_{<35}(A)\,]$ provided a better fit than either RR $(D;E)$ (dev = 13.59 – 7.28 = 6.31, $P = 0.012$) or RR$[\,D;I_{<35}(A)\,]$ (dev = 13.59 – 9.24 = 3.96, $P = 0.047$), and RR$[\,D;E,A,I_{<35}(A)\,]$ a better fit than RR $(D;E,A)$ (dev = 14.10 – 9.44 = 4.66, $P = 0.031$). Thus the observed variation in estimated ERR per Sv represented in Figs. 2 and 3 could be explained by a parameter for risk before age 35 and, for risk at higher ages, a trend in either age ATB or attained age.

Table VIII summarizes a supplemental analysis to that part of Table VII concerning the joint relationship of age ATB and attained age to dose response. The entries in the body of the table are point and interval estimates, where feasible, of ERR at 1 Sv for subjects in each cell of a matrix whose rows and columns correspond to intervals of age ATB (0–19, 20–39 and >=40) and attained age (<35, 35–44, 45–54, 55–64, 65–74 and >=75), respectively. The right-hand column corresponds to intervals of age ATB (E) adjusted for attained age (A); in the adjustment, A is treated both as a continuous variable and as filtered by an indicator $[\,I_{<35}(A)\,]$ for attained age younger than 35:

$$\mathrm{RR} = 1 + [\alpha_{0\text{–}19} I_{0\text{–}19}(E) + \alpha_{20\text{–}39} I_{20\text{–}39}(E) + \alpha_{>=40} I_{>=40}(E)\,]\, D \exp[\beta A + y I_{<35}(A)\,],$$

where the α's correspond to the tabulated ERR estimates. The bottom row of the table corresponds to intervals of attained age adjusted for age ATB as a continuous variable:

$$\mathrm{RR} = 1 + [\alpha_{<35} I_{<35}(A) + \ldots + \alpha_{>=75} I_{>=75}(A)\,]\, D \exp(\beta E].$$

The tabulated point estimates suggest, first, a marked difference between risk before and after age 35, consistent with the analysis of Table VII. There is an apparent tendency for ERR to decrease with increasing age ATB within attained age intervals and (in the right-hand column) after adjustment for attained age, but the inference is not strongly based, as indicated by the broad and overlapping confidence intervals in Table VIII as well as a comparison of deviances in Table VII.

All but 2 of the 38 breast cancer cases diagnosed before age 35 were under 20 years of age ATB. The exceptions, who were 25 and 27 years old ATB, were both diagnosed in 1951 at ages 31 and 33, respectively; the younger case had

TABLE VII

Summary of Regression Analyses for Modified Dose Response: Point Estimates with 90% Confidence Limits

Regression variable (parameter)					
D (α)	E (β_1)	$A - 50$ (β_2)	$I_{<35}(A)$ (β_3)	ln $(T/25)$ (β_4)	Dev[a] (df)
1.50	—[b]	—	.		—
(1.12, 1.94)					
3.60	–0.0374	—	—	—	7.28
(2.00, 6.35)	(–0.064, –0.014)				(1)
1.65	—	–0.0470		—	9.24
(0.42. 7.59)		(–0.079, –0.020)			(1)
1.36	—		2.30	—	9.63
(1.00, 1.78)			(1.14, 3.87)		(1)
1.52	—	–0.0322	1.64	—	13.71
(1.11, 2.01)		(–0.063, –0.006)	(0.367, 3.29)		(2)
2.07	–0.0104	–0.0381	—	—	9.44
(0.84, 4.80)	(–0.050, 0.028)	(–0.084, 0.005)			(2)
2.72	–0.0285		1.90	—	13.59
(1.44, 5.00)	(–0.056, –0.005)		(0.670, 3.60)		(2)
2.08	–0.0148	–0.0192	1.70	—	14.10
(0.84, 4.95)	(–0.056, 0.024)	(–0.065, 0.0252)	(0.404, 3.41)		(3)
1.50	—			–0.0513	0.01
(1.11, 1.96)				(–0.93, 0.89)	(1)
5.05	–0.0487	—	—	–0.980	9.42
(2.51, 10.3)	(–0.082, –0.021)			(–2.12, 0.12)	(2)
1.62		–0.0484	—	0.258	9.43
(1.18, 2.14)		(–0.081, –0.021)		(–0.700, 1.31)	(2)
1.34		—	2.34	0.160	11.71
(0.96, 1.78)			(1.16, 3.96)	(–0.771, 1.19)	(2)
3.26	–0.0341	—	1.70	–0.494	14.09
(1.52, 7.02)	(–0.066, –0.007)		(0.405, 3.41)	(–1.66, 0.677)	(3)
1.47		–0.0339	1.70	0.381	14.09
(1.05, 1.97)		(–0.066, –0.007)	(0.405, 3.43)	(–0.610, 1.50)	(3)

Note. The tabulated values are estimates and 90% confidence intervals for the parameters of special cases of the general model,

$$RR\ [D;E,A-50,\ I_{<35}(A),\ \ln(T/25)] = 1 + \alpha D \exp\ [\beta_1 E + \beta_2(A-50) + \beta_3 I_{<35}(A) + \beta_4 \ln(T/25)].$$

where D is breast tissue equivalent dose in Sv (neutron RBE = 10), E is age at the time of the bombings, A is attained age, $I_{<35}(A)$ indicates whether attained age was less than 35, T is time since exposure, and α and $\beta_1 \ldots, \beta_4$ denote unknown parameters.

[a] Improvement in deviance over model in row 1; Dev = deviance; df = degrees of freedom.

[b] Parameter value fixed at zero.

an estimated dose of 15 mSv and died in 1952, whereas the older case, who died in 1959, had an unknown dose according to both T65D and DS86. Of the remaining 36 cases, 2 had unknown doses and 7 were not exposed. For the cohort younger than 20 ATB, ERR per Sv was essentially flat as a function of attained age above 35 (Table VIII, Fig. 4) but was markedly higher at earlier ages. The drop in ERR between attained ages 30–34 and 35–49 was quite sharp, as indicated by the following regression estimates for exposed women: 16.6 (5.2, 102.8) for ages 30–34 vs 2.4 (0.9, 5.3) for 35–39. With the NIC included, the corresponding estimates were 8.3 (3.4, 19.5) and 2.7 (1.1, 5.7).

The effect of including the NIC data in the above calculations was to increase the low-dose breast cancer rate substantially at attained ages under 35 and decrease it slightly at higher ages, reducing but not eliminating the difference between the two intervals. It is by no means clear that the number of breast cancers observed before age 35 among the women exposed to low doses was particularly low compared to expectation; observed breast cancer rates, by dose group and attained age (30–34, 35–44, 45–54 and 55–64) are given in Table IX along with those expected (at zero dose) according to the Hiroshima and Nagasaki tumor registries *(19)*, and it is the NIC rates, rather than those for subjects with doses under 0.1 Gy, that seem less consistent with registry rates. Simple linear regressions on radiation dose for the above attained-age intervals for exposed subjects, adjusted for city, were used to estimate excess relative and absolute risk at 1 Sv (Table X). Also, the estimates in Fig. 4 and the zero-dose expected rates from Table IX were used to compute estimated rates at zero and 1 Sv (Fig. 5). It is interesting that the

TABLE VIII
Linear Model Estimates (with 90% Confidence Intervals) of Excess Relative Risk per Sievert, by Interval of Age ATB *(E)* and Attained Age *(A)*

	Attained age						
Age ATB	<35	35–44	45–54	55–64	65–74	>=75	Summary[a]
0–19	13.5 (4.4, 63.9)	1.5 (0.6, 2.7)	2.6 (1.5, 4.4)	1.8 (0.1, 6.2)	—	—	3.5 (0.6, 22.0)
20–39		1.3 (0.3, 0.5)	1.6 (0.8, 2.9)	1.1 (0.4, 2.2)	0.8 (–0.1, 2.6)	–	2.5 (0.3, 21.6)
>=40	—	—	—	0.01 (NC, 0.7)	0.5 (NC, 1.8)	0.8 (–0.04, 2.8)	1.1 (–0.1, 20.6)
Summary[b]	17.1 (5.1, 95.9)	1.9 (0.8, 4.1)	3.4 (1.4, 0.2)	1.9 (0.5, 6.7)	1.5 (NC, 10.0)	1.8 (NC, 19.2)	

Note. The summary column on the right is adjusted for attained age, as explained in footnote a, and the summary row at the bottom is adjusted for age ATB as explained in footnote b.

NC: Confidence limit could not be calculated.

[a]Column entries correspond to the α values in the expression,

$$RR = 1 + [\alpha_{0-19} I_{0-19}(E) + \alpha_{20-39} I_{20-39}(E) + \alpha_{>=40} I_{>=40}(E)]\ D \exp[\beta A + \gamma I_{<35}(A)]:$$

here and in footnote b, the subscripted letter I is used to denote an indicator function, equal to one if the argument falls within the interval specified by the subscript, and equal to zero otherwise.

[b]Row entries correspond to the a values in the expression.

$$RR = 1 + [\alpha_{>35} I_{>35}(A) + \ldots + \alpha_{>=75} I_{>=75}(A)]\ D \exp(\beta E)$$

observed and estimated risks at early ages were high in both absolute and relative terms. In particular, the excess absolute risk was nonsignificantly higher *(P* = 0.085) for attained ages 30–34 compared to ages 35–44. It is also clear, from Figs. 4 and 5 and Tables IX and X, that there was far less variation by attained age in terms of absolute compared to relative risk at high doses.

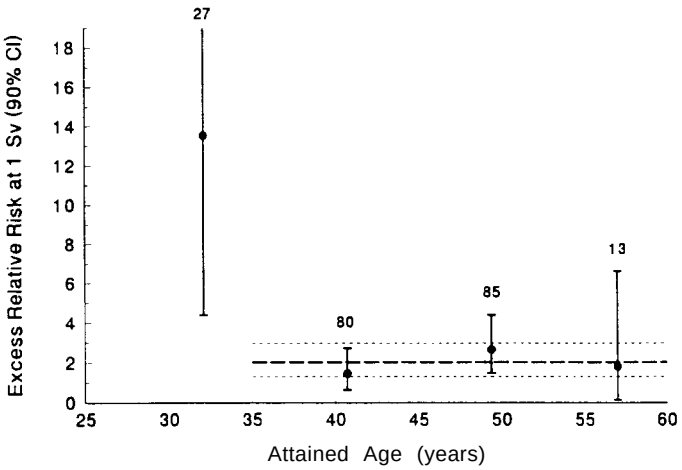

FIG. 4. Estimated excess relative risk (ERR) at 1 Sv for exposed women under age 20 at the time of the bombings (ATB), by interval of attained age (25–34, 35–44, 45–54, 55–60). Estimates and 90% confidence limits stratified on city, age ATB, attained age and period. Horizontal lines correspond to the estimate and 90% confidence limits for combined ages >=35. Total number of cases appears above the upper confidence limit for each interval of attained age.

All of the early-onset cases among women under 20 ATB were diagnosed before 1979; over half (19/36) had died by 1987. That proportion is not significantly greater than the 68 fatalities among the total of 164 cases diagnosed before 1979 in the same age cohort *(P* = 0.20). Death before 1987 was not associated with radiation dose in any of the above three subsets of cases, nor was length of survival among the deceased cases. Only 2 of the early-onset cases experienced second breast cancers before the end of follow-up, a number consistent with the 7 bilateral cases among the 164 cases under 20 years ATB diagnosed before 1979.

Year of observation for risk (equivalently, time since exposure) was not significantly related to ERR per Sv, either before or after adjustment for age ATB or attained age (Table VII). The 1990 report of the National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR V) *(20)* presented fitted estimates for breast cancer incidence based partly on data from the previous report in this series *(3)* and partly on data from two United States series *(21, 22).* The BEIR V Committee concluded that relative risk decreased with increasing time since exposure for all exposure ages, on the basis of the following fitted model,

$$RR(D; x_1, x_2, x_3, x_4) = 1 + \alpha D \exp(\Sigma \beta_i x_i). \qquad (6)$$

where $x_1 = 1$ if $E <= 15$ and zero otherwise (where E is age ATB), $x_2 = \ln(T/20)$. T is time in years since exposure,

TABLE IX

Comparison of Observed Breast Cancer Rates for Women Less than 20 Years Old at the Time of the Bombings with Those Expected, in the Absence of Exposure, According to Age-Specific Rates from the Hiroshima and Nagasaki Tumor Registries *(19)* by Exposure (Dose) Group and Attained Age: Cases per 10^5 PY

Exposure (dose) group average equivalent dose (Sv)	Attained age (year) 30–34	35–44	45–54	55–64
NIC (0 Sv)				
Observed	20.6	23.8	67.8	36.7
Expected	13.5	49.5	73.8	78.6
<0.1 Gy (0.01 Sv)				
Observed	11.1	38.8	62.4	84.1
Expected	13.6	49.1	71.4	76.2
0.1–0.49 Gy (0.28 Sv)				
Observed	72.9	56.9	120.7	53.6
Expected	13.4	47.6	75.2	82.0
0.5–1.99 Gy (1.19 Sv)				
Observed	87.0	92.5	296.7	181.2
Expected	13.6	49.2	68.4	70.5
2.0–6.0 Gy (4.35 Sv)				
Observed	221.7	302.2	405.0	829.3
Expected	13.5	49.5	75.4	76.7

$x_3 = x_2^2$ and $x_4 = (1 - x_1)(E - 15)$. The BEIR V model, fitted to the present data, provided a deviance reduction of 8.3 with 4 df over the simple linear dose–response model RR *(D)* = 1 + α *D*. This compares with reductions of 7.3 and 9.2 with 1 df obtained for the simpler models R *(D;E)* and R *(D;A)*, respectively (presented in Table VII and displayed in Figs. 2 and 3), and 13.6 and 13.7 with 2 df for R [$D;E,I_{<35}(A)$] and R [$D;A,I_{<35}(A)$], respectively. Thus the complexity of the BEIR V model seems unnecessary to explain these data.

DISCUSSION

The present series differs from the previous one *(3)* in that new subjects, exposed in Nagasaki to comparatively low doses, were added to the study population and their cases were added to the series. That, and 5 more years of follow-up, increased the number of cases by nearly half, and doubled the number of second breast cancers. Also, a new dosimetry system was introduced. It is noteworthy that the conclusions of the previous series remain essentially unchanged and have been strengthened in many respects. In particular, the dose response in the present data was highly significant statistically, and strongly linear. Quadratic curvature corresponding to crossover doses lower than 5 Sv could be ruled out at a (one-sided) confidence level of 95%. This result is inconsistent with the International Commission on Radiological Protection model *(23)*, which postulates a dose and dose-rate reduction factor of two between risk per sievert at (about) 1.5 Sv and near zero, at least to the extent that the factor may have been based upon the assumption of an upward-concave, quadratic dose–response model. Lack of evidence of curvilinearity for the breast cancer dose response is not particularly new, of course; in the 1980 BEIR Report, breast cancer was noted as an exception to the committee's "preferred" linear-quadratic model *(24)*. As expected, all of the above findings are highly consistent with those presented in the recent tumor registry report *(15)*, in spite of the various differences in approach between the two studies.

The most remarkable finding from the previous series was an excess breast cancer risk in adult life after radiation exposure at age less than 10 years. Now, on the basis of 68

TABLE X

Relative and Absolute Measures of Excess Risk, by Attained Age: Simple, Age-Specific, Linear Regression Coefficients with 90% Confidence Limits, Adjusted for City; Exposed Women Only, under 20 Years Old at the Time of the Bombings

Excess risk at 1 Sv	Attained age (years) 30–34	35–44	45–54	55–60
Relative risk	14.0 (4.5, 70)	1.4 (0.6, 2.7)	2.7 (1.5, 4.5)	1.8 (0.1, 6.9)
Cancers per 10^4 PY	12.2 (6.7, 20)	5.6 (2.7, 9.3)	17.2 (11, 25)	12.8 (1.0, 34)

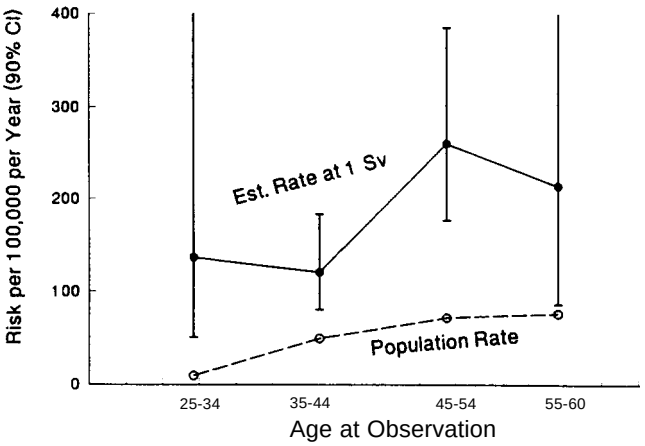

FIG. 5. Expected and estimated breast cancer risk at zero and 1 Sv, respectively, by attained age for women younger than 20 years ATB.

cases in all, including 58 exposed women with DS86 dose estimates, that finding has been confirmed; it can be seen to apply both to women under 5 and between 5 and 10 years old ATB. It is also highly relevant that further follow-up of the Rochester population of women who had been irradiated during infancy to shrink their thymus glands has continued to provide new evidence of a radiation-related excess risk *(10).* In the present study, the estimated ERR per Sv was nonsignificantly greater after exposure at ages 0–9 ATB than after exposure at ages 10–19 and contributed to a significant decreasing trend in risk with increasing age ATB. At this point, there can be little doubt that radiation exposure of breast tissue during early childhood and infancy can contribute to the risk of breast cancer during adult life.

One of the relatively few differences between the present study and earlier studies of this population pertains to risk after exposure at ages over 40. The previous studies found no evidence of excess risk, whereas in the present study there was a marginally significant excess risk. The evolution of estimates of excess risk over time for the subcohort 40–49 ATB, in particular, is of some interest; a significantly negative estimate was obtained from the 1950–1974 data, the estimate was zero for the 1950–1980 series, and the estimate was positive at a suggestive level of significance for the present series. No explanation for this variation, other than small-number statistics, is required; breast cancer risk is and has been low in Japan, especially for the generations born before or around the turn of the century *(19, 25),* and the radiation-related excess risk in that cohort does not appear to be large. The present study evidences an excess risk after exposure at ages above 40, but one that is relatively small compared to that associated with exposure at earlier ages. Because women 40 years old or older ATB were at least 80 years old in 1985, subsequent follow-up studies of this population are likely to yield little new information on risk in that birth cohort.

The implications of the new finding for medical practice, and for the use of mammography in particular, are minimal. For a two-view, screen-film mammography with grid, the mean dose for glandular tissue has recently been reported to be 2.8 mGy *(26).* At that dose, for a Japanese population exposed at age 40 or older, the estimated excess relative risk based on our findings is 0.001, or 0.1%, with 90% CI of 0, 0.3%.

The possible modifying effects of age ATB or, alternatively, attained age on the carcinogenic effects of ionizing radiation have important implications for radiation protection and risk estimation, as well as for our understanding of underlying biological mechanisms. Kellerer and Barclay *(27)* have pointed out that age-related variation in excess cancer mortality among A-bomb survivors, usually modeled as a decline in excess RR per Sv with increasing age ATB, can be expressed equally well as a declining function of attained age. Attained age and age ATB are highly correlated, even with over 35 years of follow-up, as indicated in Table III. An important message of Tables VII and VIII is the lack of a statistical basis at present for separating the effects of the two factors. The practical importance of the relative effects of age ATB and attained age stems from two considerations: First, at the present stage of follow-up, lifetime risk as predicted by fitted models in which ERR per Sv depends upon either age ATB or attained age, but not both, may differ as much as fivefold. That is, if the ERR among the youngest age-ATB cohorts, which tends to be high, remains unchanged throughout the remainder of these survivors' life spans, their total excess risk will be much higher than if, in the future, their ERR should decline to values presently observed among persons exposed when older. Second, it is important to know whether young people are especially sensitive to radiation carcinogenesis and should therefore receive increased protection.

The biological implications of the relative effects of age ATB and attained age are more profound. For simplicity, the following discussion is couched in terms of a two-stage model. If, for example, undifferentiated breast cells are more vulnerable to cancer initiation than differentiated cells, exposure during childhood and adolescence should involve more risk at (say) age 70 than exposure at age 40, simply because the proportion of undifferentiated cells normally decreases with increasing age *(28).* The foregoing argument involves the reasonable assumption that an already-initiated, but untransformed, cell is equally likely, at age 70, to have developed into a detectable cancer whether initiation occurred at age 10 or age 40. But one might also argue that, given a radiation exposure at age 10, the *relative* likelihood of breast cancer due to that exposure, vs an exposure to some other initiator, must decrease with increasing age because of the increasing likelihood, with increasing age, that cancer initiation may have already occurred due to exposure to other agents. Both

hypotheses are plausible, and it is more reasonable to ask which (if either) process is the dominant one, rather than which is more likely to be true.

A potentially important *a posteriori* finding of the present study is that, among women exposed before age 20, the radiation-related excess risk of early-onset breast cancer, i.e., before age 35, was several times higher in relative terms than the excess risk for breast cancer diagnosed at later ages. The evidence of Fig. 4 and Tables VIII and X raises doubts about the adequacy of models, like R *(D;E)*, in which ERR, after a minimal latent period, is constant over time since exposure, although the model seems tenable enough for risk at ages 35 and older. But to conclude simply, on the basis of Table X for example, that risk may be modeled more efficiently in terms of absolute risk is to miss the point. Mathematical models like R *(D;E)* correspond to a biological model in which radiation exposure acts as a cancer initiator and in which later, age-related events are required before an initiated cell begins its progression to a detectable cancer. If possible, we should use the present finding as a clue to ways of investigating the biological basis for radiation carcinogenesis.

A genetically based breast cancer risk before age 40 or 45, involving germ-line p53 tumor-suppressor gene mutations, is known to be associated with Li-Fraumeni syndrome *(29, 30)*. Specific loci on the q arm of chromosome 17 have been associated with family history of breast cancer and with breast cancer at early ages in particular *(31, 32)*. Swift *et al. (33)* have argued that heterozygosity for ataxia telangiectasia (AT) is associated with a greatly increased risk for breast cancer associated with medical X-ray exposure; the epidemiological basis for that particular claim is open to question *(34–36)*, but the possibility cannot be ruled out that AT heterozygotes may be at increased risk of radiation-induced cancer *(37)*. Hereditary retinoblastoma patients are known to be at increased risk of osteosarcoma; among patients treated by radiation, risk of osteosarcoma within the radiation field is especially high *(38)*.

Clearly, the present finding demands an intensive investigation of the early-onset cases in terms of family history of cancer and physical evidence of mutations in tumor and normal tissue. Initially, it may seem somewhat puzzling that unusually high sensitivity to radiation carcinogenesis (if such it be) should manifest itself in increased risk before age 35 and not at later ages; for women under 20 ATB there was a remarkable drop in ERR per Sv between the 5-year age intervals 30–34 and 35–39, whereas ERR was approximately constant over the age interval 35–60. A high risk in a small, and unidentified, minority of exposed women, however, might not be detectable except at ages of low baseline risk. Thus, even if affected women experienced similarly high radiation-related risks at later ages, that risk might not be apparent. Except for the early-onset cases, these data are consistent with a model in which ERR may depend upon age ATB but not upon time since exposure. That is, women exposed to radiation have more breast cancer than women who are not exposed, but their excess risk appears to occur no earlier or later than expected according to age-specific baseline rates. The existence in this population of a small, genetically susceptible subgroup with a large excess risk, which follows the population pattern in terms of constancy of RR over time, could produce the pattern seen in Fig. 3.

It should be noted that the distribution of bilateral cases between the group with early-onset cancers and the remainder of the group of cases under 20 ATB, and the similar dose responses for bilateral and unilateral breast cancer do not themselves suggest the existence of a sensitive subgroup, in which bilateral cancers might be expected to be frequent, especially at high radiation doses. Twenty second cancers, 9 of them among women under 20 years ATB, may not be enough to be informative, however.

Alternatively, there might be a genetic subgroup with heightened sensitivity to radiation-induced breast cancer specifically of the early-onset type. Weak evidence for this possibility may be found in Table X, which shows that the estimated absolute excess risk was (nonsignificantly) greater before ages 30–34 than at ages 35–44. Such a subgroup might have a different temporal pattern of risk because expression of the radiation-induced damage for them might depend less upon promotional events after exposure; there is some evidence of a different pattern of age-specific rates for (presumably) non-radiation-related breast cancers among persons genetically prone to higher risk *(39)*. The most promising prospect for testing the existence of a possible heritable susceptibility factor awaits the cloning of candidate genes, like BRCA-1; a reasonable approach would be to evaluate mutation spectra in normal and tumor tissue from breast cancer cases, using a four-way design contrasting high-dose vs low-dose cases within early-onset and later-onset groups.

Another hypothesis with some similarities to the one just mentioned is that radiation may usually act as an initiator but occasionally may act at later stages in the carcinogenic process, whether in a susceptible subgroup or in the population as a whole; the occasional effect would be evident only at ages when baseline rates were low. Thus exposure might occasionally hasten the appearance of an already-initiated cancer (which otherwise might appear if affected by other factors or, in their absence, might never appear) whether initiation was caused by the same radiation exposure or by something else. If the phenomenon occurred in the general population, unusual patterns of familial risk would not be expected, although there might conceivably be unusual changes at the molecular level in tumor tissue from high-dose, early-onset cases.

A relevant observation is that no evidence was found of increased risk of early-onset breast cancer among women 20–29 years old ATB (a woman 30 or older ATB would of course be over 35 by the time follow-up began in 1950). It may be that the minimal latent period for radiation-induced breast cancer is 10–15 years, even among unusually susceptible women. Another possibility is that heightened susceptibility to radiation-induced breast cancer is modified by the first full-term pregnancy. The average age at first full-term pregnancy among women 20–29 ATB was 24 *(40)*, and it is conceivable that women exposed to radiation before their first pregnancy might be at higher risk of radiation-induced breast cancer than women exposed to similar radiation doses, at similar ages, but after their first pregnancy.

The observed breast cancer pattern in Fig. 4 is reminiscent of a similar finding for mortality from all cancers except leukemia, and from stomach cancer in particular, among survivors under 10 ATB in the 1950–1985 LSS mortality report *(4)*. There, the ERR for attained ages 20–29 was several times higher than that for attained ages 30–49, but the values for the intervals 30–39 and 40–49 were similar. Estimates of absolute excess risk, however, increased with increasing attained age. In the mortality report *(4)*, the finding was evaluated as evidence for a radiation-related shortening of the latent period for those exposed when young, and in the 1988 report of the United Nations Scientific Committee on the Effects of Atomic Radiation *(41)* (Annex F, paragraph 88) it was interpreted as a significant decline in dose-specific ERR over time after exposure. Neither of these interpretations directly addresses biological issues, but each has implications for risk estimation. The observed pattern, like that for breast cancer in the present study, could reflect the existence of either a susceptible subgroup or a relatively rare type of radiation effect in the general population; each possibility, upon further study, may lead to testable hypotheses that themselves have certain specific implications for risk estimation and projection, as well as for cancer biology.

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REFERENCES

1. D. H. McGregor, C. E. Land, K. Choi, S. Tokuoka, P. I. Liu, T. Wakabayashi and G. W. Beebe, Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1969. *J. Natl. Cancer Inst.* **59,** 799–811 (1977).
2. M. Tokunaga, J. E. Norman, Jr., M. Asano, S. Tokuoka, H. Ezaki, I. Nishimori and Y. Tsuji, Malignant breast tumors among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1974. *J. Natl. Cancer Inst.* **62,** 1347–1359 (1979).
3. M. Tokunaga, C. E. Land, T. Yamamoto, M. Asano, S. Tokuoka, H. Ezaki and I. Nishimori, Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1980. *Radiat. Res.* **112,** 243–272 (1987).
4. Y. Shimizu, H. Kato and W. J. Schull, Studies of the mortality of A-bomb survivors. 9. Mortality, 1950–1985: Part 2. Cancer mortality based on the recently revised doses (DS86). *Radiat. Res.* **121,** 120–141 (1990).
5. W. C. Roesch, Ed., *U.S.–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki—Final Report*, Vol. 1. Radiation Effects Research Foundation, Hiroshima, 1987.
6. W. C. Roesch, Ed., *U.S.–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki—Final Report*, Vol. 2. Radiation Effects Research Foundation, Hiroshima, 1987.
7. G. W. Beebe and M. Usagawa, *The Major ABCC Samples*. TR 12–68. Atomic Bomb Casualty Commission, Hiroshima, 1968.
8. M. Tokunaga, C. E. Land, T. Yamamoto, M. Asano, S. Tokuoka, H. Ezaki and I. Nishimori, Breast cancer in Japanese A-bomb survivors (Letter). *Lancet* **2,** 924 (1982).
9. N. G. Hildreth, R. E. Shore and L. H. Hempelmann, Risk of breast cancer among women receiving radiation treatment in infancy for thymic enlargement. *Lancet* **II,** 273 (1983).
10. N. G. Hildreth, R. E. Shore and P. M. Dvoretsky, The risk of breast cancer after irradiation of the thymus in infancy. *N. Engl. J. Med.* **321,** 1281–1284 (1989).
11. M. Tokunaga, K. Mabuchi, H. Kate, K. Shimaoka and C. E. Land, *Guidelines for the Conduct of Site-Specific Cancer Incidence Studies among A-bomb Survivors, Hiroshima and Nagasaki.* RP 9-88, Radiation Effects Research Foundation, Hiroshima, 1988.
12. S. Tokuoka, M. Asano, T. Yamamoto, M. Tokunaga, G. Sakamoto, W. H. Hartmann, R. V. P. Hutter, C. E. Land and D. E. Henson, Histologic review of breast cancer cases in survivors of atomic bombs in Hiroshima and Nagasaki, Japan. *Cancer* **54,** 849–854 (1984).
13. J. G. Azzopardi, O. F. Chepick, W. H. Hartmann, N. A. Jafary, A. Llombart-Bosch, L. Ozzello, S. Rilke, N. Sasano, L. H. Sobin, S. C. Sommers, H. Stralsberg, J. Sugar and A. O. Williams, The World Health Organization histological typing of breast tumours—second edition. *Am. J. Clin. Pathol.* **78,** 806–816 (1982).
14. Japan Mammary Cancer Society: General rule for clinical and histological record of mammary cancer. *Jpn. J. Surg.* **5,** 118–122 (1977).
15. D. E. Thompson, K. Mabuchi, E. Ron, M. Soda, M. Tokunaga, S. Ochikubo, S. Sugimoto, T. Ikeda, M. Terasaki, S. Zumi and D. L. Preston, Cancer incidence in atomic bomb survivors. Part II. Solid tumors. 1958–1987. *Radiat. Res.* **137,** S17–S67 (1994).
16. D. L. Preston, J. H. Lubin and D. A. Pierce, *Epicure User's Guide.* HiroSoft International, Seattle, 1991.
17. G. W. Beebe, H. Kato and C. E. Land, Studies of the mortality of A-bomb survivors. IV. Mortality and radiation dose, 1950–1966. *Radiat. Res.* **48,** 613–649 (1971).
18. C. K. Wanebo, K. G. Johnson, K. Sato and T. W. Thorslund, Breast cancer after exposure to the atomic bombings of Hiroshima and Nagasaki. *N. Engl. J. Med.* **279,** 667–671 (1968),
19. D. M. Parkin, C. S. Muir, J. Waterhouse, S. L. Whelan, Y. T. Gao, J. Ferlay and J. Powell, Cancer *Incidence in Five Continents,* Vol. VI.

Scientific Publication No. 120, International Agency for Research on Cancer, Lyon, 1992.

20. National Research Council, Committee on the Biological Effects of Ionizing Radiations, *Health Effects of Exposure to Low Levels of lonizing Radiatiom (BEIR V).* National Academy Press, Washington, DC, 1990.

21. R. E. Shore, N. Hildreth, E. Woodard, P. Dvoretsky, L. Hempelmann and B. Pasternack, Breast cancer among women given X-ray therapy for acute postpartum mastitis. *J. Natl. Cancer Inst.* **77,** 689–696 (1986).

22. Z. Hrubec, J. D. Boice, Jr., R. R. Monson and M. Rosenstein, Breast cancer after multiple chest fluoroscopies: Second follow-up of Massachusetts women with tuberculosis. *Cancer Res.* **49,** 229–234 (1989).

23. ICRP, *1990 Recommendations of the International Commission on Radiological Protection.* Publication 60. *Annals of the ICRP,* Vol. 21, Nos. 1–3, Pergamon, London, 1991.

24. National Research Council, Committee on the Biological Effects of Ionizing Radiations, *Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR III).* National Academy Press, Washington, DC, 1980.

25. M. Segi, S. Tominaga, K. Aoki and I. Fujimoto, Eds., *Cancer Mortality and Morbidity Statistics—Japan and the World.* Japan Scientific Press, Tokyo, 1981.

26. J. G. Kereiakes, G. Simmons, G. Barnes and A. Haus, Relationships between image quality and radiation dose in nuclear medicine and X-ray imaging. In *Radiation Protection in Medicine:* Proceedings of the 28th Annual Meeting, 1–2 April, 1992 (A. K. Poznanski. Ed.), pp. 39–63, National Council on Radiation Protection and Measurements, Bethesda, MD, 1993.

27. A. M. Kellerer and D. Barclay, Age dependencies in the modeling of radiation carcinogenesis. *Radiat. Prot. Dosim.* **41,** 273–282 (1992).

28. J. Russo, B. A. Gusterson, A. E. Rogers, I. H. Russo, S. R. Wellings and M. J. van Zwieten, Comparative study of human and rat mammary tumorigenesis. *Lab. Invest.* **62,** 244–278 (1990).

29. F. P. Li and J. F. Fraumeni, Jr., Soft-tissue sarcomas, breast cancer, and other neoplasms: a familial syndrome? *Ann. Intern. Med.* **71,** 747–752 (1969).

30. F. P. Li, J. E. Garber, S. H. Friend, L. C. Strong, A. F. Patenaude, E. T. Juengst, P. R. Reilly, P. Correa and J. F. Fraumeni, Jr., Recommendations on predictive testing for germ line p53 mutations among cancer-prone individuals. *J. Natl. Cancer Inst.* **84,** 1156–1160 (1992).

31. M-C. King, Breast cancer genes: how many, where and who are they? *Nature Genet.* **2,** 89–90 (1992).

32. J. M. Hall, L. Friedman, C. Guenther, M. K. Lee, J. L. Weber, D. M. Black and M-C. King, Closing in on a breast cancer gene on Chromosome 17q. *Am. J. Hum. Genet.* **50,** 1235–1242 (1992).

33. M. Swift, D. Morrell, R. B. Massey and C. L. Chase, Incidence of cancer in 161 families affected by ataxia telangiectasia. *N. Engl J. Med.* **325,** 1831–1836 (1991).

34. J. D. Boice, Jr. and R. M. Miller, Risk of breast cancer in ataxia telangiectasia (Letter to the Editor). *N. Engl. J. Med.* **326,** 1357–1358 (1992).

35. E. J. Hall, C. R. Geard and D. J. Brenner, Risk of breast cancer in ataxia telangiectasia (Letter to the Editor). *N. Engl. J. Med.* **326,** 1358–1359 (1992).

36. C. E. Land, Risk of breast cancer in ataxia telangiectasia (Letter to the Editor). *N. Engl. J. Med.* **326,** 1359–1360 (1992).

37. E. Ron and B. Modan, Thyroid and other neoplasms following childhood scalp irradiation. In *Radiation Carcinogenesis: Epidemiology and Biological Significance* (J. D. Boice, Jr. and J. F. Fraumeni, Jr., Eds.), pp. 139–151. Raven Press, New York, 1984.

38. C. Eng. F. P. Li, D. H. Abramson, R. M. Ellsworth, F. L. Wong, M. B. Goldman, J. Seddon, N. Tarbell and J. D. Boice, Jr., Mortality from second tumors among long-term survivors of retinoblastoma. *J. Natl. Cancer Inst.* **85,** 1121–1128 (1993).

39. E. B. Claus, N. Risch and W. D. Thompson, Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am. J. Hum. Genet.* **48,** 232–242 (1991).

40. C. E. Land, N. Hayakawa, S. Machado, Y. Yamada, M. C. Pike, A. Akiba and M. Tokunaga, A case-control interview study of breast cancer among Japanese A-bomb survivors: I. Main effects. *Cancer Causes Control* **5,** 157–165 (1994).

41. UNSCEAR, *Sources, Effects and Risks of Ionizing Radiation. Annex F, Radiation Carcinogenesis in Man.* United Nations, New York, 1988.